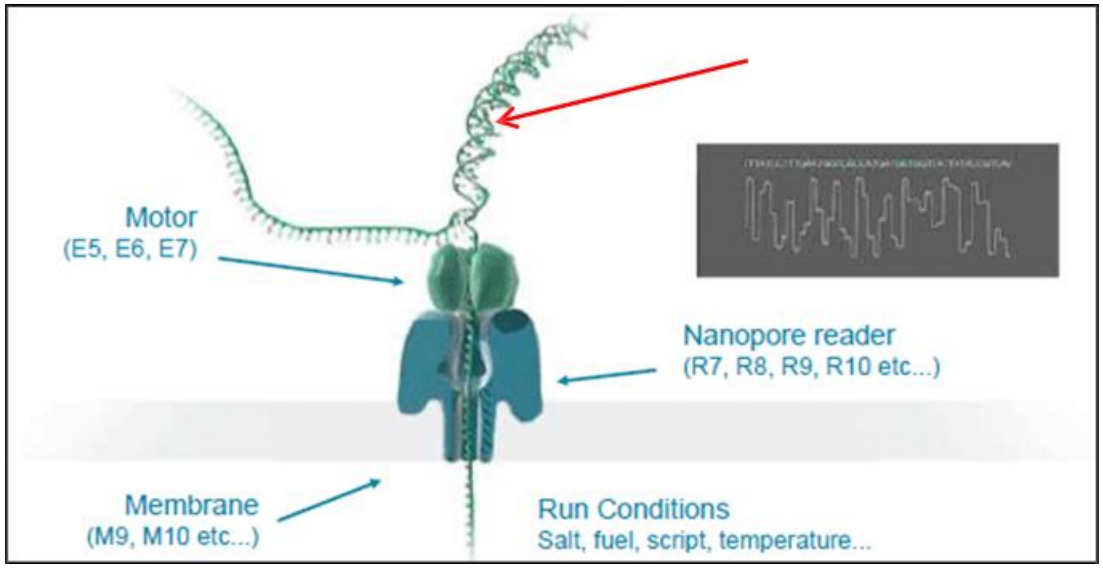
EXHIBIT 2

EXHIBIT 2: INFRINGEMENT OF U.S. PATENT NO. 9,546,400 BY OXFORD NANOPORE'S MINION AND PROMETHION DEVICES

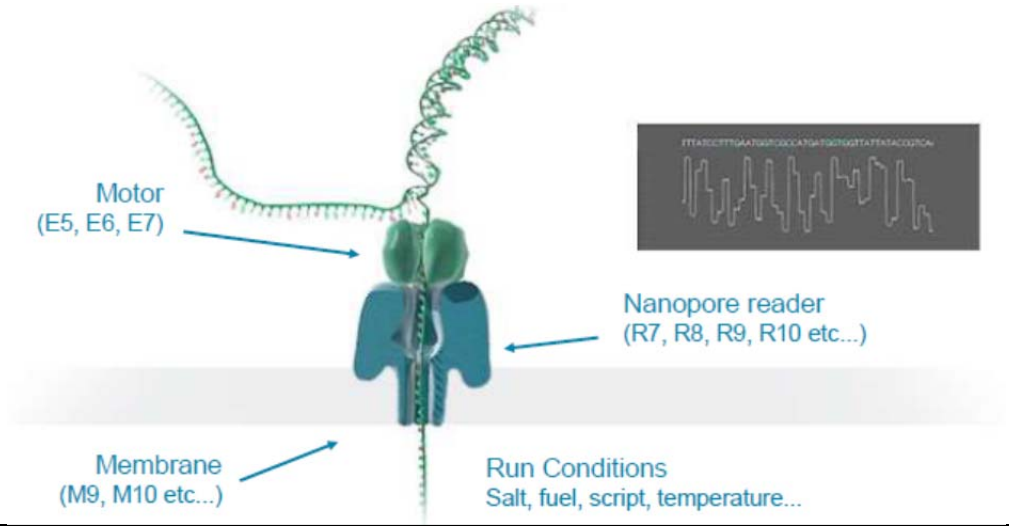
On information and belief, the PromethION device performs the same function as the MinION device. *See* Appendix A, Exhibit 8 at 1:26 ("The PromethION contains all the same technology as the MinION."). Thus, the evidence listed below describing the PromethION device is equally applicable to the MinION device and vice versa.

	Claim 1:	
1	A method for sequencing a nucleic acid template comprising:	The PromethION and MinION devices sequence nucleic acid molecules. For example, according to Oxford's website, the PromethION "offers real time, long read high fidelity DNA and RNA sequencing." Appendix A, Exhibit 1; *see also*, *e.g.*, Appendix A, Exhibit 2 at 51 (describing the PromethION instrument as a "sequencing module"); Appendix A, Exhibit 3 (describing the PromethION instrument as follows: "DNA sequencing: the system may process the sample until a minimum of tenfold read coverage over specified regions of interest has been seen, until a specific mutation has been observed in a sample or until enough sequence data has been collected to reliably assemble a sample against a reference.")
a)	providing a substrate comprising a nanopore in contact with a solution, the solution comprising a template nucleic acid above the nanopore;	Use of PromethION and MinION devices for sequencing includes providing a nanopore in contact with a solution containing template nucleic acid. For example, the nanopore sequencing process employed in the PromethION and MinION devices is depicted as contacting a nanopore with a nucleic acid molecule, here, a deoxyribonucleic acid ("DNA") molecule, by feeding the nucleic acid molecule through the nanopore from above the nanopore:

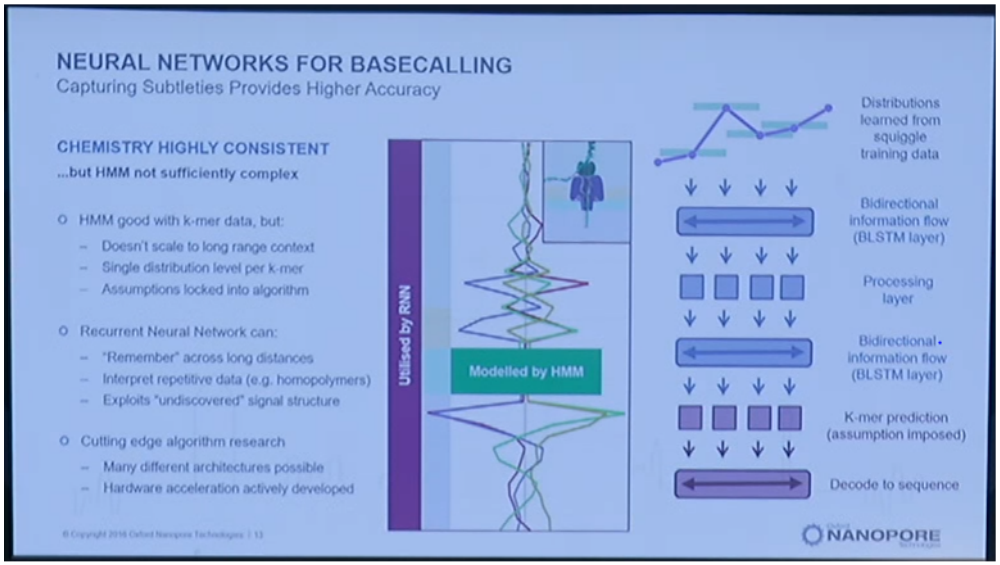
PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 1:	
		 Appendix A, Exhibit 2 at 30 (red arrow indicates nucleic acid supplied to the nanopore).
b)	providing a voltage across the nanopore;	The MinION and PromethION devices perform a single-molecule sequencing process using an electrochemical system, which involves providing a voltage across the nanopore. For example, Oxford's nanopore sequencing technology that is integrated in the MinION and PromethION devices has been characterized as follows: "In the Oxford nanopore system, the nanopore is inserted into a membrane created by a synthetic polymer. This membrane has very high electronic resistance. Here, you can see a nanopore piercing a single hole in the membrane made from synthetic polymer. A potential is applied across the membrane, resulting in a current flowing only through the aperture of the nanopore." Appendix A, Exhibit 5 at 0:40 –1:02. This "current flowing only through the aperture of the nanopore" is driven by a voltage (i.e., "a potential") across the nanopore. *Id.*

PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 1:	
c)	measuring a property which has a value that varies for N monomeric units of the template nucleic acid in the pore, wherein the measuring is performed as a function of time, while the template nucleic acid is translocating through the nanopore, wherein N is three or greater; and	Use of the PromethION and MinION devices for sequencing includes measuring the property of a particular combination of multiple bases as the template nucleic acid translocates through the nanopore. For example, in the Oxford nanopore system, a nucleic acid, DNA, is sequenced as it passes through the nanopore. Appendix A, Exhibit 5 at 1:19. "As the DNA strand moves through the nanopore one base at a time, a characteristic disruption in current is created by the presence of particular combinations of bases in a particular part of the nanopore." *Id.* at 1:45 – 1:58. This characteristic disruption in current, caused by three or more nucleotides residing in the nanopore, is measured by the nanopore reader depicted below. Appendix A, Exhibit 7 ("As a DNA strand is fed through a nanopore by a processive enzyme, the *trinucleotides* in contact with the pore are detected through electrochemistry.") (emphasis added); s*ee* Appendix A, Exhibit 9. Because these disruptions in current are so specific to the different combinations, this information can be used to determine the order of bases on that DNA strand." Appendix A, Exhibit 5 at 1:45 – 1:58. 

PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

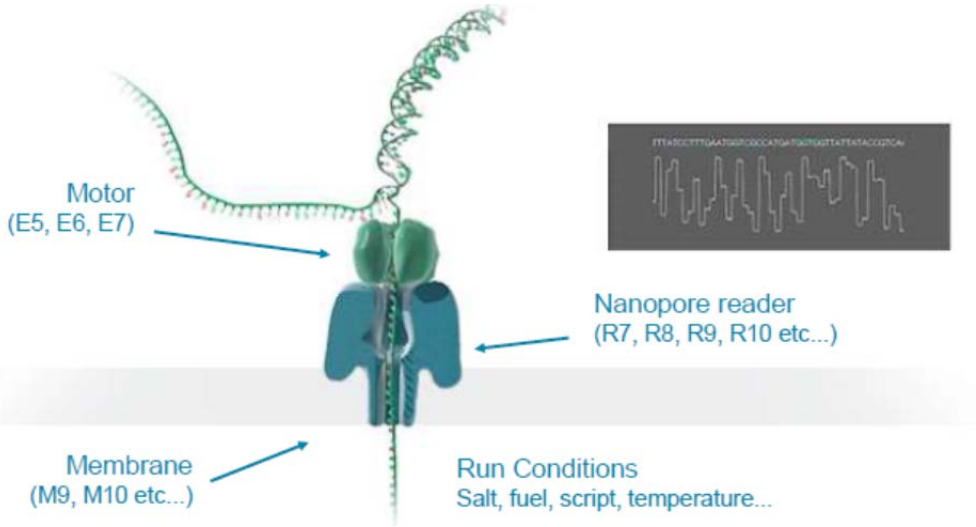
	Claim 1:	
		Appendix A, Exhibit 2 at 30 (depicting nanopore reader measuring disruptions in current caused by the translocation of N nucleotides through the nanopore).
d)	determining the sequence of the template nucleic acid using the measured property from step (c) by performing a process including comparing the measured property from step (c) to calibration information produced by measuring such property for 4 to the N sequence combinations.	Use of the PromethION and MinION devices for sequencing includes determining the sequence of the template nucleic acid by comparing the measured property of the particular combinations of bases as they translocate through the nanopore calibration data. The comparison is done using an artificial neural network trained to recognize the characteristic disruptions in current created by the presence of particular combinations of bases in a particular part of the nanopore:  Appendix A, Exhibit 10; Appendix A, Exhibit 11 at 14:08.

PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 1:	
		Clive Brown, Chief Technical Officer for Oxford Nanopre, described the neural networks used for basecalling in the PrometION and MinION devices: "We move one base at a time in one direction and we get these so-called 'squiggles.' And then for a long time we were using an HMM to decode those and most of you know that recently we've changed the underlying algorithm to use something called a recurrent neural network." Appendix A, Exhibit 11 at 3:36. "All it means is its got a memory. It has a time-based memory. *Id.* at 13:43. "In essence, at the moment, what we have to do is we take squiggle, we have to align it to answer ["Distributions learned from squiggle training data"], and label the squiggle. And then we use these methods to learn the mapping of squiggle:answer. On the network, given input will then emit k-mers and we then find the likeliest path through the k-mers and decode it into sequence. That's the version you've got right now. That's how it works." *Id.* at 14:40 The above description corresponds to comparing the measured property from step (c) ("the squiggles") to calibration information produced by measuring the characteristic disruption in current for 4 to the N sequence combinations ("the answer" or "Distributions learned from squiggle training data") to decode the emitted k-mers into sequence.

	Claim 2:	
2.	The method of claim 1 wherein a property in step (c) comprises current.	Use of the PromethION and MinION devices for sequencing includes measuring the "characteristic disruption in current [that] is created by the presence of particular combinations of bases in a particular part of the nanopore" as the template nucleic acid translocates through the nanopore. Appendix A, Exhibit 5 at 1:45 – 1:58. For example, in the Oxford nanopore system, a nucleic acid, DNA, is sequenced as it passes through the nanopore. *Id.* at 1:19. "As the DNA strand moves through the nanopore one base at a time, a characteristic disruption in current is created by the presence of particular combinations of bases in a particular part of the nanopore." *Id.*

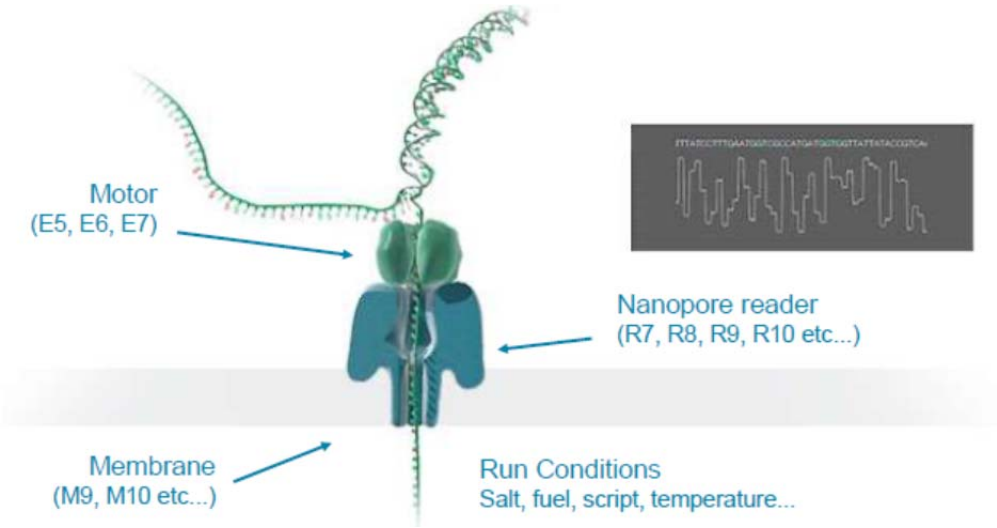
PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 2:	
		at 1:45 – 1:58. This characteristic disruption in current, caused by three or more nucleotides residing in the nanopore, is measured by the nanopore reader depicted below. Appendix A, Exhibit 7 ("As a DNA strand is fed through a nanopore by a processive enzyme, the *trinucleotides* in contact with the pore are detected through electrochemistry.") (emphasis added); s*ee* Appendix A, Exhibit 9. Because these disruptions in current are so specific to the different combinations, this information can be used to determine the order of bases on that DNA strand." Appendix A, Exhibit 5 at 1:45 – 1:58.  Appendix A, Exhibit 2 at 30 (depicting nanopore reader measuring disruptions in current caused by the translocation of N nucleotides through the nanopore).

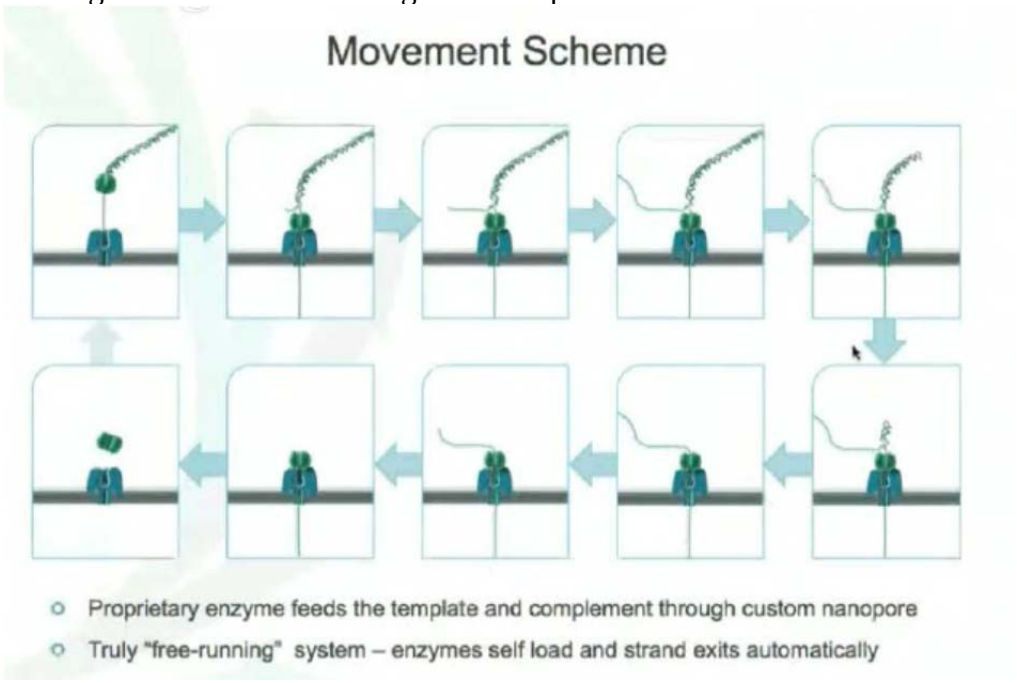
	Claim 3:	
3.	The method of claim 1 wherein the translocation through the pore is driven by the applied voltage.	The MinION and PromethION devices perform a single-molecule sequencing process using an electrochemical system, which involves applying a voltage. For example, Oxford's nanopore sequencing technology that is integrated in the MinION and PromethION devices has been characterized as follows:

PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 3:	
		"In the Oxford nanopore system, the nanopore is inserted into a membrane created by a synthetic polymer. This membrane has very high electronic resistance. Here, you can see a nanopore piercing a single hole in the membrane made from synthetic polymer. A potential is applied across the membrane, resulting in a current flowing only through the aperture of the nanopore." Appendix A, Exhibit 5 at 0:40 –1:02. This potential across the membrane contributes to translocation of the DNA through the pore.

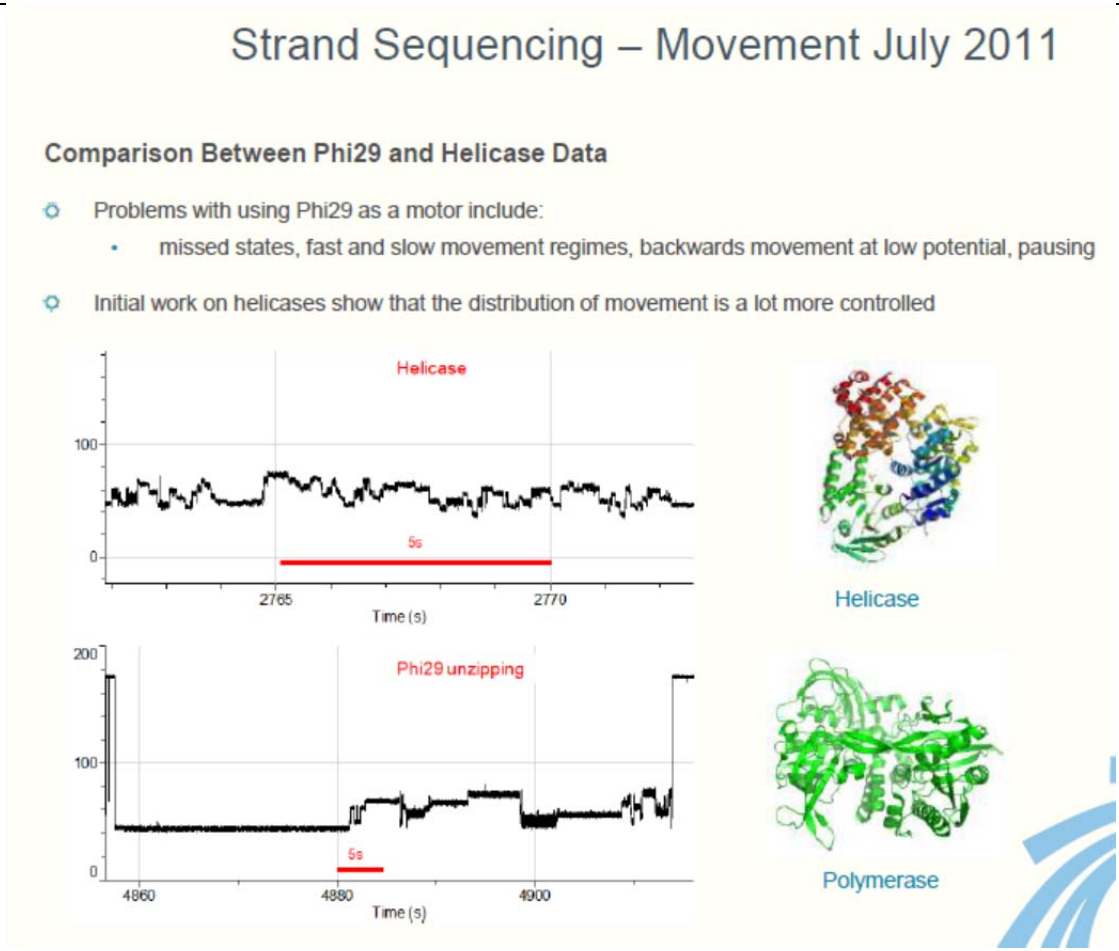
	Claim 4:	
4.	The method of claim 1 wherein the translocation rate through the pore is enzymatically controlled.	Use of the PromethION and MinION devices for sequencing includes using an enzyme to control the translocation rate of a nucleic acid through the nanopore. For example, the figure below depicts the use of a DNA enzyme complex to move a single strand of DNA through the nanopore at a rate of "one base at a time" –  Appendix A, Exhibit 2 at 30. "The enzyme [or motor], shown in green, is designed to ratchet the DNA strand through the nanopore one base at a time. The enzyme binds to

	Claim 4:	
		the end of a double-stranded DNA and unzips the double strand to form a long single strand which it feeds through the nanopore." Appendix A, Exhibit 5 at 1:25 – 1:45; *see* Appendix A, Exhibit 11 at 3:36 ("From our point of view, the motor was one of the really key, key things to make this work. You need step-wise, unidirectional control of motion to stand a chance of doing de novo base calling.")

	Claim 5:	
5.	The method of claim 3 wherein the translocation through the pore is controlled by a polymerase, a helicase, a translocase, a viral genome packaging motor, or a chromatin remodeling complex.	Use of the PromethION and MinION devices for sequencing includes using a "proprietary enzyme" to control the translocation of a nucleic acid through the nanopore. For example, the figure below depicts the use of a DNA enzyme complex to move a single strand of DNA through the nanopore –  Appendix A, Exhibit 4 at 14:01 ("Proprietary enzyme feeds the template and

	Claim 5:	
		complement through custom nanopore."). "The enzyme, shown in green, is designed to ratchet the DNA strand through the nanopore one base at a time. The enzyme binds to the end of a double-stranded DNA and unzips the double strand to form a long single strand which it feeds through the nanopore." Appendix A, Exhibit 5 at 1:25 – 1:45; *see* Appendix A, Exhibit 11 at 3:36 ("From our point of view, the motor was one of the really key, key things to make this work. You need step-wise, unidirectional control of motion to stand a chance of doing de novo base calling.") Specifically, Oxford has tested the use of both helicases and Phi29, a polymerase to control the translocation of the nucleic acid template through the nanopore:

PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 5:	
		 Appendix A, Exhibit 2 at 20; see also Appendix A, Exhibit 6 ("Different classes of enzymes used" as "motors.")

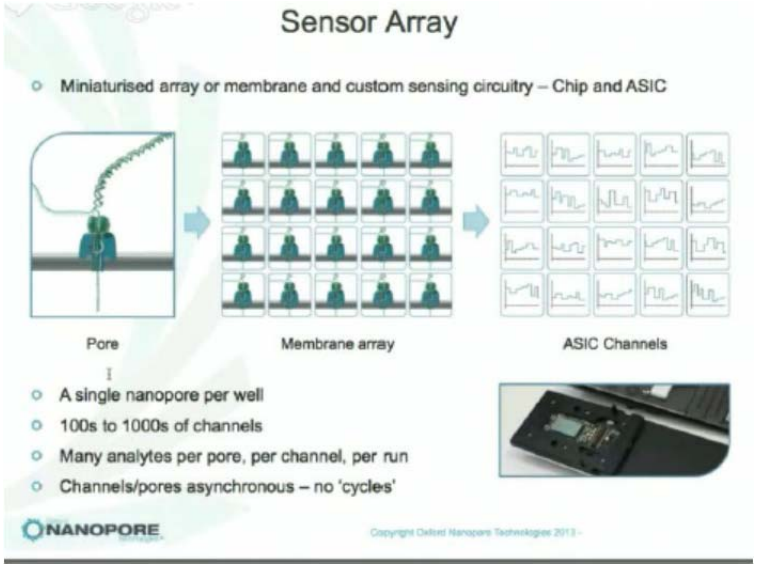
PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 6:	
6	The method of claim 1, where in N corresponds to n-mers comprising 3-mers, 4-mers or 5-mers.	Oxford nanopore technology can measure the characteristic disruption in current generated by N monomeric units of a template nucleic acid in a pore, where N is three or greater. In fact, "Oxford nanopore designs and manufactures bespoke nanopore structures for a range of applications." Appendix A, Exhibit 5 at 0:30 – 0:36. This range of applications includes designing nanopores that can read the signals generated by 3 or greater nucleotides located within a certain part of a nanopore. *See, e.g.*, Appendix A, Exhibit 9.

	Claim 7:	
7.	The method of claim 6 wherein N corresponds to n-mers comprising 3-mers.	Oxford nanopore technology can measure the characteristic disruption in current generated by N monomeric units of a template nucleic acid in a pore, where N is three or greater. In fact, "Oxford nanopore designs and manufactures bespoke nanopore structures for a range of applications." Appendix A, Exhibit 5 at 0:30 – 0:36. This range of applications includes designing nanopores that can read signals generated by 3 or greater nucleotides located within a certain part of a nanopore. *See* Appendix A, Exhibit 7 ("As a DNA strand is fed through a nanopore by a processive enzyme, the *trinucleotides* in contact with the pore are detected through electrochemistry.") (emphasis added); Appendix A, Exhibit 9.

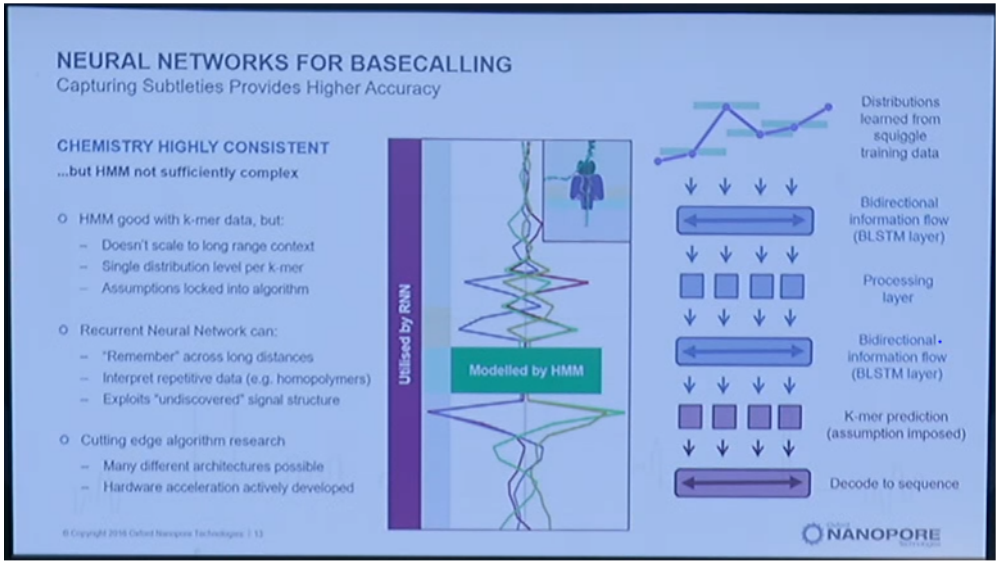
	Claim 8:	
8.	The method of claim 1 wherein the method is carried out on an array of nanopores in the substrate.	The use of PromethION and MinION includes sequencing nucleic acids using an array chip. "To create a high throughput system, a number of nanopore experiments can be conducted at the same time using an array chip. Multiple microwells are fabricated onto an array chip using standard semiconductor materials. These array chips may be scaled according to need. The user may require 10s of channels to 100s of thousands of channels depending on the application. This array chip is built into a consumable cartridge which also contains the fluidics required to run the chip. The analyte is added to the cartridge, which is then used in conjunction with an instrument, the GridION node, for real-time data collection and analysis." Appendix A, Exhibit 5 at 2:26 – 3:04.

PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 8:	
		 Appendix A, Exhibit 4 at 15:28.

	Claim 10:	
10.	The method of claim 1 wherein the comparing process comprises examining a lookup table for each of the 4 to N combinations, and keeping only those meeting a threshold value.	Use of the PromethION and MinION devices for sequencing includes determining the sequence of the template nucleic acid by comparing the measured property of the particular combinations of bases as they translocate through the nanopore to calibration data. The comparison is done using an artificial neural network trained to recognize the characteristic disruptions in current created by the presence of particular combinations of bases in a particular part of the nanopore:

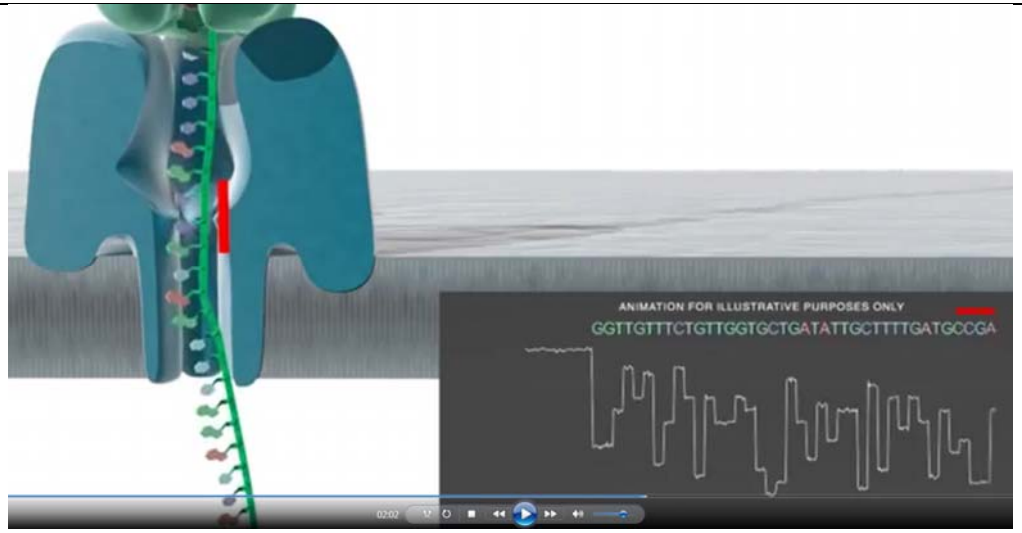
PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 10:	
		 Appendix A, Exhibit 10; Appendix A, Exhibit 11 at 14:08. Clive Brown, Chief Technical Officer for Oxford Nanopore, described the neural networks used for basecalling in the PrometION and MinION devices: "We move one base at a time in one direction and we get these so-called 'squiggles.' And then for a long time we were using an HMM to decode those and most of you know that recently we've changed the underlying algorithm to use something called a recurrent neural network." Appendix A, Exhibit 11 at 3:36. "All it means is its got a memory. It has a time-based memory." *Id.* at 13:43. "In essence, at the moment, what we have to do is we take squiggle, we have to align it to answer ["Distributions learned from squiggle training data"], and label the squiggle. And then we use these methods

	Claim 10:	
		to learn the mapping of squiggle:answer. On the network, given input will then emit k-mers and then we find the likeliest path through the k-mers and decode it into sequence. That's the version you've got right now. That's how it works." *Id.* at 14:40 The above description encompasses the use of calibration information produced by measuring the characteristic disruption in current for 4 to the N sequence combinations ("the answer" or "Distributions learned from squiggle training data") as a look-up table to decode the emitted k-mers into sequence.

	Claim 14:	
14.	The method of claim 1 wherein N corresponds to n-mers comprising 4-mers	Oxford nanopore technology can measure the characteristic disruption in current generated by N monomeric units of a template nucleic acid in a pore, where N is three or greater. In fact, "Oxford nanopore designs and manufactures bespoke nanopore structures for a range of applications." Appendix A, Exhibit 5 at 0:30 – 0:36. For example, the figure below illustrates one such "bespoke nanopore structure" that can measure the signals generated by 4 nucleotides (4-mers) within a certain part of the nanopore and use that information to generate corresponding sequencing information -

PLAINTIFFS' INITIAL CLAIM CHART FOR U.S. PATENT NO. 9,546,400

	Claim 14:	
		 Appendix A, Exhibit 9 (red bars illustrating that an Oxford nanopore can measure the characteristic disruption in current generated by 4 nucleotides and use that information to identify the corresponding nucleotide sequence).

	Claim 15:	
15.	The method of claim 1 wherein N corresponds to n-mers comprising 5-mers.	Oxford nanopore technology can measure the characteristic disruption in current generated by N monomeric units of a template nucleic acid in a pore, where N is three or greater. In fact, "Oxford nanopore designs and manufactures bespoke nanopore structures for a range of applications." Appendix A, Exhibit 5 at 0:30 – 0:36. This range of applications includes designing nanopores that can read the signals generated by 3 or greater nucleotides within a certain part of a nanopore. *See* Appendix A, Exhibit 7 ("As a DNA strand is fed through a nanopore by a processive enzyme, the *trinucleotides* in contact with the pore are detected through electrochemistry.") (emphasis added); s*ee* Appendix A, Exhibit 9.